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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P65922PC00	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/NL 03/00583	International filing date *(day/month/year)* 14.08.2003	Priority date *(day/month/year)* 14.08.2002
International Patent Classification (IPC) or both national classification and IPC A61P35/00		
Applicant ERASMUS UNIVERSITY MEDICAL CENTER ROTTERDAM et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 8 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11.03.2004	31.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Covone-van Hees, M.G Telephone No. +31 70 340-4416

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NL 03/00583

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-92 as originally filed

Claims, Numbers

1-51 received on 29.11.2004 with letter of 29.11.2004

Drawings, Sheets

1/2-2/2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority in written form.

   ☒ furnished subsequently to this Authority in computer readable form.

   ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 30-32,39-41 (as to I.A.) 28

   because:

   ☒ the said international application, or the said claims Nos. 30-32,39-41 (as to I.A.) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 28

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-7,9-27,29-43,46,47,50,51
	No:	Claims	1,8,44,45,48,49
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-27,29-51
Industrial applicability (IA)	Yes:	Claims	1-27,29,33-38,42-51
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 30-32,39-41 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents:

D1: LI J ET AL: "Leukaemia disease genes: Large-scale cloning and pathway predictions" NATURE GENETICS, NATURE AMERICA, NEW YORK, US, vol. 23, no. 3, November 1999 (1999-11), pages 348-353, ISSN: 1061-4036

D2: WO 01/77340 A (MERCK PATENT GMBH ;DUECKER KLAUS (DE)) 18 October 2001 (2001-10-18)

D3: WO 99/38525 A (BIOGEN INC ;TSIAGBE VINCENT (US); BROWNING JEFFREY (US); THORBECKE) 5 August 1999 (1999-08-05)

2 **Art. 5 PCT**

2.1 The subject-matter of claim 1 does not meet the requirements of Art.5 PCT. The subject-matter concerned is the reference to genomic regions with Celera identification codes. The information of a sequence listing, which is part of the content of a database referred to by an accession number, is regularly annotated and up-dated. Due to these modifications, a sequence listing corresponding to the content of a database characterised by an accession number can vary over time and cannot be considered as reliable information. Moreover the operations of presently available data institutions are not designed and maintained in a way which meets certain more specialised needs of the patenting procedure, notably in relation to establishing the precise nature of the disclosure made on a certain date. The mere indication of an accession number results in problems relating to legal certainty i.e. to the sufficiency of the original disclosure according to Art.5 PCT, since if an original sequence turns out to be incorrect later on,

the invention may not be reduced to practice on the basis of that earlier incorrect version. Consequently, the scope of present claim cannot be ascertain in a direct and unambiguous way.

3 **Art. 5 and 6 PCT**

3.1 As far as it concerns genomic regions identified by means of a gene symbol, unless the skilled person can unambiguously identify said genomic region (and the corresponding encoded polypeptide) the definition lacks clarity. In present case the gene symbol is considered to be an internal designation, which in itself conveys no technical information for the skilled person. Thus, these definitions are unclear in the sense of Art.6 PCT. Moreover, since said gene symbol refers only to an identification code and not to a sequence listing, this definition lacks disclosure, the reasons being the same, mutatis mutandis, as remarked under point 2.1.

4 **NOVELTY** (Art.33(2)PCT)

4.1 D1 discloses a method to identify putative genes involved in tumour development (especially leukaemia) by means of retroviral insertional mutagenesis. This method comprises at least all the steps of the method disclosed in claims 46a-e and 47. A list of genes identified with said method is available in the document (see the whole article).

4.2 D2 identifies a dual specificity phosphatase (DUSP10) polypeptide and discloses the amino acid and nucleic acid sequence of the polypeptide. DUSP10 is involved in the development of e.g. leukemia, therefore its use in diagnosis and antagonists thereto to treat tumours is suggested. Recombinant vectors and host cells are claimed (see pg.1 l.28- pg.2 l.14; pg.13 l.22-pg.14 l.11; pg.16 l.26-26; pg.19 l.26-32; claims). D2 anticipates the subject-matter of claims 48 and 49 which is therefore not new (Art.33(2) PCT).

4.3 D3 discloses composition for the treatment of a subject having follicular lymphoma to block the interaction of LT-beta with its receptor (e.g. soluble receptor or antibodies) (see pg.5 l.26 - pg.6 l.8 and ex. 1). D3 is detrimental to the novelty of the subject-matter of claims 44,45, 48 and 49.

4.4 The above-mentioned lack of disclosure and clarity notwithstanding, the subject-matter of claim 1 is not new in the sense of Art. 33(2) PCT, and therefore the criteria of Art. 33(1) PCT are not met. The applicant has deleted, in the amendments filed with the

letter dated 29.11.04, reference to the genomic regions: dual specificity phosphatase (DUSP10) and LT-beta (claim 1), conflicting with the documents cited in the search report D2 and D3. In view of the available prior art the subject-matter of claim 1 therefore appears to comply with the requirements of Art.33(2) PCT. However in the description (see pg.25 lines 5-8), the applicant himself underlines that "a large number of the murine genomic regions disclosed in table 1 encode known genes". Most of the genes disclosed in table 1 have been incorporated in claim 1. Polypeptide encoded by said genomic regions are implicitly disclosed if the genomic region per se is known. The fact that the applicant considers to be the first to have established that these genomic regions may be involved in cancer does not render said genomic regions novel.

4.5 The same arguments cited for claim 1 are valid, mutatis mutandis, for claim 8 of the application.

5 **Inventive Step** Art.33(3) PCT

5.1 In case the applicant amends claim 1 in order to formally overcome the objections under Art.33(2) PCT, the subject-matter of claim 1 is not based on an inventive step. It is not apparent on which basis an inventive concept may be acknowledge considering that the claim 1 refers to "the use of genomic region ..... for the preparation of polypeptide encoded by said region". The preparation of a polypeptide from a genomic region is described in the text-books and is part of the common knowledge of every skilled person in this technical field. The subject-matter of claim 1 lacks therefore inventiveness (Art.33(3) PCT).

5.2 The subject-matter of claim 2 refers to the use of genomic regions listed in cl.1 for the preparation of an inhibitor. a) The term "inhibitor" lacks clarity (Art.6 PCT) and merely amounts to a statement of the underlying problem, without providing the technical features necessary for solving the problem. b) if the genomic regions referred to in claim 1 do not comply with the requirements of Art.5 and/or 6 PCT also inhibitors fail to comply the same Article. c) for well known genes, inhibitors, (the lack of clarity not withstanding) are straightforward products for a skilled person. Only specific inhibitors (but no example is given in the application) may overcome the objection under Art.33(3) PCT.

5.3 The same arguments cited for claim 2 are valid, mutatis mutandis, for claim 15 of the application.

5.4 As far as it concerns the subject-matter of claims 23,25,29,30,32,33,35,38,39,43

referring to a method of treatment, diagnosis, and pharmaceutical or diagnostic compositions, in the absence of any working example in the application, the applicant fails to show that any of the product is suitable for said purpose and solve the problem of the claim. In present case, it is considered that the mere listing of genes which may be involved in cancer (leukemia) does not imply that related products (e.g. inhibitors etc) are effective to treat or diagnose cancer. Moreover none of the products is exemplified in the application. Consequently present claims lack inventiveness (Art.33(3) PCT).

5.5 The subject-matter of independent claims 8,10-14,44 is not inventive since they are mainly standard products and methods in this technical field, which fall within the routine skills of those in the art, and which do not appear to lead to any surprising effects or advantages.

5.6 Claim 46 has been amended in order to cite that step f) is "directly" after step e). This definition is not characterised by technical features, but by means of the result to be achieved, without providing the technical features on how this result has been achieved. This definition lacks therefore clarity (Art.6 PCT).

5.7 Moreover, there is doubt if the subject-matter of claim 46 is based on an inventive step (Art.33(3) PCT). Document D1 is considered to represent the most relevant state of the art (see point 4.1 for the summary). The subject-matter of claim 46 differs in that the sequencing has been directly after the step e) in claim 46. The problem to be solved by the present invention may therefore be regarded as providing alternatives to the sequencing step. The sequencing step is indeed considered, in the method to identify genomic regions, a cumbersome step, for which the skilled person is looking for alternatives. The applicant provide as solution "direct sequencing". However the solution proposed in claim 46 step f) of the present application cannot be considered as involving an inventive step (Art. 33(3) PCT). As noted above, the wording of the claim does not provide the technical features on how this result is achieved. Moreover, the examples of the application all comprise a further step (either CsCl or cloning) after claim 46 step e). Therefore they cast doubt on how the applicant achieves a direct sequencing and if he solves the problem of the claim. Consequently the subject-matter of claim 46 does not comply with the requirements of Art.33(3) PCT because there are serious doubts that it solves the problem mentioned in the claim.

5.8 Dependent claims 3-7,9,12-14,16-22,24,26,27,31,34,36,37,40-42,45,47,49-51 do not

contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step, since they are either anticipated by D2 and D3 or they do not lead to any unexpected features or properties.

6 For the assessment of the present claims 30-32,39-41 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

7 **Final Remarks**

7.1 The attention of the applicant is drawn to the fact that the objections at point 2.1 and 3.1 cannot be overcome by reference/deposit to a new sequence listing. In this respect, a sequence listing furnished at present stage of the file would be considered as added subject-matter since there is no basis for such an amendment of the application as originally filed. As a principle - independent of the fact whether the sequence listing did or did not change in the different versions- incorporations of sequence listings deriving from references, which are per definition not invariant, are not considered to be allowable under Art.34(2)(b) PCT.

7.2 Moreover genes involved in the development of cancer are known in the art. The subject-matter of clam 1, comprising putative alternative genes involved in cancer, may not fulfill the requirements of unity of invention under the PCT and corresponding EPC regulation (in case the applicant enters at EPO for the regional phase). Each gene may represent a different solution not linked by a common novel and inventive special technical feature. The question a lack of compliance with Rule 13 PCT has not been raised, due to main deficiencies under Art.5,6,33(2) and (3) PCT of the subject-matter of claim 1. However, the question of unity may arise in the regional or national phase.